



# EXHIBIT A

**EXHIBIT A:  
AMENDMENTS MADE TO PENDING CLAIMS  
U.S. PATENT APPLICATION SERIAL NO. 09/493,353  
(ATTORNEY DOCKET NO. 2094/1E286-US1)**

**SUBMITTED PURSUANT TO 37 C.F.R. § 1.121(c)(1)(ii)**

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13. (Amended) A method as defined in claim [10] 12, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB)

<SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB)

<SEQ ID NO. 12> when said forward primer is (C131F25) or

(C143F26); and

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB)

<SEQ ID NO. 11> when said forward primer is (C69F28).

42. (Twice amended) An oligonucleotide probe [comprising a sequence] selected from the group consisting of:

5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11>;

5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>;

5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13>;

5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

# **EXHIBIT B**

they are earned. Nintendo complains that Mr. Willis' analysis is the equivalent of assuming royalty payments were made on a daily basis, and that his method artificially inflates prejudgment interest by \$15,000,000. Alpex responds that its calculation conservatively estimates a quarterly royalty payment schedule, and that such a schedule is reasonable in light of the fact that Nintendo's own license agreements generally specified such payments. To make its point, Alpex compares the prejudgment interest resulting from its mid-year calculation with higher figures allegedly resulting from a quarterly payment assumption. Unfortunately, as Nintendo points out, Alpex's comparison is misleading because it fails to keep the effective annual rates constant for purposes of both the mid-year calculation and the quarterly calculation. Therefore, I cannot conclude that Alpex's mid-year convention accurately approximates a quarterly payment schedule. I believe that it is fully within my discretion to accept the more straightforward, year-end calculation proposed by Nintendo.

To summarize, I find that an award of prejudgment interest is warranted. Such interest shall be calculated on an after-tax, year-end basis at the commercial paper rate. According to the testimony of Mr. Sherwin, which I accept as authoritative, prejudgment interest on the jury's verdict through August 1, 1994 is \$37,220,311. Interest on the jury's verdict from August 1, 1994 to the date of judgment will be addressed by Mr. Sherwin in the supplemental affidavit ordered herein. In addition, Alpex is entitled to interest on the 6% royalties payable on Nintendo's infringing revenues between December 1, 1992 and May 31, 1994. Within 21 days of the date hereof, Nintendo shall submit a supplemental affidavit by Mr. Sherman, or such other qualified expert, specifying prejudgment interest (calculated in accordance with the ruling herein) on royalties payable on its infringing revenues between December 1992 and May 1994.

### CONCLUSION

For the reasons set forth above, the court denies Nintendo's motions for judgment of non-infringement and judgment of invalidity as a matter of law; the court denies Nintendo's motion for a new trial on liability; and the court also denies Nintendo's motion for a remittitur, new trial, or judgment as a matter of law with respect to damages. Alpex's motion for entry of judgment is granted in part and denied in part. Specifically, the court grants Alpex's motion for an account-

ing with respect to Nintendo's infringing revenues between December 1, 1992 and May 31, 1994. Judgment shall be entered in an amount that, in addition to the jury's award, includes 6% of Nintendo's infringing revenues during the period between December 1, 1992 and May 31, 1994. The court also grants Alpex's motion for pre-judgment interest, directing that such interest be calculated on year-end royalty payments, and on an after-tax basis, using the commercial paper rate, as proposed by Nintendo. Alpex shall also be entitled to prejudgment interest on the 6% of Nintendo's infringing revenues between December 1, 1992 and May 31, 1994, to be determined through the aforementioned accounting. Finally, the court denies Alpex's motion for a 50% enhancement of the jury's verdict. Within 21 days of the date hereof, Nintendo shall submit (1) an accounting of its infringing revenues between December 1, 1992 and May 31, 1994, and (2) a supplemental affidavit specifying the prejudgment interest on the 6% royalty payments due on these additional revenues. Within one week of Nintendo's submission, the parties shall submit a joint proposed judgment in accordance with the court's ruling herein. In the event that the parties fail to agree upon a joint proposed judgment, they shall each submit a proposed judgment for the court's consideration.

SO ORDERED.

### U.S. Court of Appeals Federal Circuit

In re Deuel

No. 94-1202

Decided March 28, 1995

### PATENTS

#### 1. Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§115.0903.03)

Existence of general method of isolating cDNA or DNA molecules is essentially irrelevant to question of whether specific molecules themselves would have been obvious, in absence of other prior art that suggests claimed DNAs, nor does fact that general process can be conceived in advance for preparing undefined compound mean that claimed specific compound was precisely envisioned and therefore obvious; Board of Patent Appeals and Interferences thus erred by rejecting claims for isolated and purified

DNA and cDNA molecules (parin-binding growth factors) alleged obviousness of method of molecules, since applied references or suggest claimed cDNA mole

Appeal from the U.S. Patent and Trademark Office, Board of Patent Interferences; 33 USPQ2d 144

Application for patent filed by Deuel, Yue-Sheng Li, Ned R. Peter G. Milner, serial no. 07/542,232. From decision of the Board of Patent Appeals and Interferences affirming the final rejection of claims, appeal. Reversed.

G. Harley Blosser and Donald S. Senniger, Powers, Leavitt & Louis, Mo., for appellants.

Donald S. Chisum, of Morrison, Seattl, Wash.; Debra A. Sherrin & Foerster, Palo Alto; Robert P. Blackburn, Emeritus, for amicus curiae The Biotechnology Association and The Bioscience Center.

Teddy S. Gron, acting associate; Albin F. Drost, acting solicitor; J. Linck, office of the solicitor, Va., for appellee.

Before Archer, chief judge, Nicol, circuit judges.

Lourie, J.

Thomas F. Deuel, Yue-Sheng Li, and Peter G. Milner ("Deuel") appeal from the November 1993 decision of the U.S. Patent and Trademark Office Board of Patent Interferences affirming the explicit rejection of claims 4-7 of application No. 07/542,232, entitled "Heating Factor," as unpatentable on ground of obviousness under 35 U.S.C. § 103 (1988). *Ex parte Deuel*, 33 U.S.P.Q.2d (Bd. Pat. App. Int. 1993). Because the Board erred in concluding that Deuel's claims directed to specific cDNA molecules have been obvious in light of the references, and no other basis is in the record to support the rejection of claims 4 and 6 generically to possible DNA molecules coding for closed proteins, we reverse.

### BACKGROUND

The claimed invention relates to isolated and purified DNA and cDNA

respect to Nintendo's infringing between December 1, 1992 and 1994. Judgment shall be entered in that, in addition to the jury's finding 6% of Nintendo's infringing during the period between December 2 and May 31, 1994. The court

Alpex's motion for pre-judgment recting that such interest be calculated on royalty payments, and on a basis, using the commercial practice proposed by Nintendo. Alpex is entitled to prejudgment interest of Nintendo's infringing revenues between December 1, 1992 and May 31, 1994, determined through the afore-accounting. Finally, the court denies the motion for a 50% enhancement of its verdict. Within 21 days of the filing, Nintendo shall submit (1) an accounting of its infringing revenues between December 1, 1992 and May 31, 1994, supplemental affidavit specifying prejudgment interest on the 6% royalty due on these additional revenues. (2) Within one week of Nintendo's submission, Alpex shall submit a joint proposed judgment in accordance with the court's ruling. In the event that the parties fail to submit a joint proposed judgment, they shall submit a proposed judgment for consideration.

ORDERED.

#### U.S. Court of Appeals Federal Circuit

In re Deuel

No. 94-1202

Decided March 28, 1995

**Obviousness/Validity — Obviousness —  
prior art — Particular inven-  
tion §115.0903.03)**

Use of general method of isolating DNA molecules is essentially irrelevant to question of whether specific molecules would have been obvious, in light of other prior art that suggests cDNAs, nor does fact that general method can be conceived in advance for pre-defined compound mean that specific compound was precisely identified therefore obvious; Board of Patent Appeals and Interferences thus erred by its claims for isolated and purified

DNA and cDNA molecules encoding heparin-binding growth factors based upon alleged obviousness of method of making molecules, since applied references do not teach or suggest claimed cDNA molecules.

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences; 33 USPQ2d 1445.

Application for patent filed by Thomas F. Deuel, Yue-Sheng Li, Ned R. Siegel, and Peter G. Milner, serial no. 07/542,232). From decision of the Board of Patent Appeals and Interferences affirming examiner's final rejection of claims, applicants appeal. Reversed.

G. Harley Blosser and Donald G. Leavitt, of Senniger, Powers, Leavitt & Roedel, St. Louis, Mo., for appellants.

Donald S. Chisum, of Morrison & Foerster, Seattle, Wash.; Debra A. Shetka, of Morrison & Foerster, Palo Alto, Calif.; and Robert P. Blackburn, Emeryville, Calif., for amicus curiae The Biotechnology Industry Association and The Bay Area Bioscience Center.

Teddy S. Gron, acting associate solicitor, Albin F. Drost, acting solicitor, and Nancy J. Link, office of the solicitor, Arlington, Va., for appellee.

Before Archer, chief judge, Nies and Lourie, circuit judges.

Lourie, J.

Thomas F. Deuel, Yue-Sheng Li, Ned R. Siegel, and Peter G. Milner (collectively "Deuel") appeal from the November 30, 1993 decision of the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences affirming the examiner's final rejection of claims 4-7 of application Serial No. 07/542,232, entitled "Heparin-Binding Growth Factor," as unpatentable on the ground of obviousness under 35 U.S.C. § 103 (1988). *Ex parte Deuel*, 33 USPQ2d 1445 (Bd. Pat. App. Int. 1993). Because the Board erred in concluding that Deuel's claims 5 and 7 directed to specific cDNA molecules would have been obvious in light of the applied references, and no other basis exists in the record to support the rejection with respect to claims 4 and 6 generically covering all possible DNA molecules coding for the disclosed proteins, we reverse.

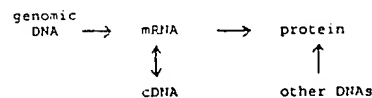
#### BACKGROUND

The claimed invention relates to isolated and purified DNA and cDNA molecules

encoding heparin-binding growth factors ("HBGFs").<sup>1</sup> HBGFs are proteins that stimulate mitogenic activity (cell division) and thus facilitate the repair or replacement of damaged or diseased tissue. DNA (deoxyribonucleic acid) is a generic term which encompasses an enormous number of complex macromolecules made up of nucleotide units. DNAs consist of four different nucleotides containing the nitrogenous bases adenine, guanine, cytosine, and thymine. A sequential grouping of three such nucleotides (a "codon") codes for one amino acid. A DNA's sequence of codons thus determines the sequence of amino acids assembled during protein synthesis. Since there are 64 possible codons, but only 20 natural amino acids, most amino acids are coded for by more than one codon. This is referred to as the "redundancy" or "degeneracy" of the genetic code.

DNA functions as a blueprint of an organism's genetic information. It is the major component of genes, which are located on chromosomes in the cell nucleus. Only a small part of chromosomal DNA encodes functional proteins.

Messenger ribonucleic acid ("mRNA") is a similar molecule that is made or transcribed from DNA as part of the process of protein synthesis. Complementary DNA ("cDNA") is a complementary copy ("clone") of mRNA, made in the laboratory by reverse transcription of mRNA. Like mRNA, cDNA contains only the protein-encoding regions of DNA. Thus, once a cDNA's nucleotide sequence is known, the amino acid sequence of the protein for which it codes may be predicted using the genetic code relationship between codons and amino acids. The reverse is not true, however, due to the degeneracy of the code. Many other DNAs may code for a particular protein. The functional relationships between DNA, mRNA, cDNA, and a protein may conveniently be expressed as follows:



Collections ("libraries") of DNA and cDNA molecules derived from various spe-

<sup>1</sup> For a more extensive discussion of recombinant DNA technology, see *In re O'Farrell*, 853 F.2d 894, 895-99, 7 USPQ2d 1673, 1674-77 (Fed. Cir. 1988); *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

cies may be constructed in the laboratory or obtained from commercial sources. Complementary DNA libraries contain a mixture of cDNA clones reverse-transcribed from the mRNAs found in a specific tissue source. Complementary DNA libraries are tissue-specific because proteins and their corresponding mRNAs are only made ("expressed") in specific tissues, depending upon the protein. Genomic DNA ("gDNA") libraries, by contrast, theoretically contain all of a species' chromosomal DNA. The molecules present in cDNA and DNA libraries may be of unknown function and chemical structure, and the proteins which they encode may be unknown. However, one may attempt to retrieve molecules of interest from cDNA or gDNA libraries by screening such libraries with a gene probe, which is a synthetic radiolabelled nucleic acid sequence designed to bond ("hybridize") with a target complementary base sequence. Such "gene cloning" techniques thus exploit the fact that the bases in DNA always hybridize in complementary pairs: adenine bonds with thymine and guanine bonds with cytosine. A gene probe for potentially isolating DNA or cDNA encoding a protein may be designed once the protein's amino acid sequence, or a portion thereof, is known.

As disclosed in Deuel's patent application, Deuel isolated and purified HBGF from bovine uterine tissue, found that it exhibited mitogenic activity, and determined the first 25 amino acids of the protein's N-terminal sequence.<sup>2</sup> Deuel then isolated a cDNA molecule encoding bovine uterine HBGF by screening a bovine uterine cDNA library with an oligonucleotide probe designed using the experimentally determined N-terminal sequence of the HBGF. Deuel purified and sequenced the cDNA molecule, which was found to consist of a sequence of 1196 nucleotide base pairs. From the cDNA's nucleotide sequence, Deuel then predicted the complete amino acid sequence of bovine uterine HBGF disclosed in Deuel's application.

Deuel also isolated a cDNA molecule encoding human placental HBGF by screening a human placental cDNA library using the isolated bovine uterine cDNA clone as a probe. Deuel purified and sequenced the human placental cDNA clone, which was found to consist of a sequence of 961 nucleotide base pairs. From the nucleotide se-

quence of the cDNA molecule encoding human placental HBGF, Deuel predicted the complete amino acid sequence of human placental HBGF disclosed in Deuel's application. The predicted human placental and bovine uterine HBGFs each have 168 amino acids and calculated molecular weights of 18.9 kD. Of the 168 amino acids present in the two HBGFs discovered by Deuel, 163 are identical. Deuel's application does not describe the chemical structure of, or state how to isolate and purify, any DNA or cDNA molecule except the disclosed human placental and bovine uterine cDNAs, which are the subject of claims 5 and 7.

Claims 4-7 on appeal are all independent claims and read, in relevant part, as follows:

4. A purified and isolated DNA sequence consisting of a sequence encoding human heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Ala ... [remainder of 168 amino acid sequence].

5. The purified and isolated cDNA of human heparin-binding growth factor having the following nucleotide sequence:

GTCAAAGGCA ... [remainder of 961 nucleotide sequence].

6. A purified and isolated DNA sequence consisting of a sequence encoding bovine heparin binding growth factor of 168 amino acids having the following amino acid sequence:

Met Gln Thr ... [remainder of 168 amino acid sequence].

7. The purified and isolated cDNA of bovine heparin-binding growth factor having the following nucleotide sequence:

GAGTGGAGAG ... [remainder of 1196 nucleotide sequence].

Claims 4 and 6 generically encompass all isolated/purified DNA sequences (natural and synthetic) encoding human and bovine HBGFs, despite the fact that Deuel's application does not describe the chemical structure of, or tell how to obtain, any DNA or cDNA except the two disclosed cDNA molecules. Because of the redundancy of the genetic code, claims 4 and 6 each encompass an enormous number of DNA molecules, including the isolated/purified chromosomal DNAs encoding the human and bovine proteins. Claims 5 and 7, on the other hand, are directed to the specifically disclosed cDNA molecules encoding human and bovine HBGFs, respectively.

During prosecution, the examiner rejected claims 4-7 under 35 U.S.C. § 103 as unpatentable over the combined teachings of Boh-

len<sup>3</sup> and Maniatis.<sup>4</sup> The Bohlen discloses a group of protein factors designated as heparin-binding proteins ("HBBMs") useful in tissue repair and promoting the formation, and repair of tissue, particularly in the brain. Bohlen isolated three HBBMs from human and bovine brain. The HBBMs have respective molecular weights of 15 kD, 16 kD, and 18 kD. Bohlen determined the first 19 amino acids of the N-terminal sequences of the HBBMs and found them to be identical for human and bovine HBBMs.<sup>5</sup> Bohlen teaches that the HBBMs are brain-specific, and suggests that they may be homologous between species. Bohlen provides no teaching of a DNA or cDNA coding for HBBMs.

Maniatis describes a method for isolating cDNAs or cDNAs by screening a cDNA library with a gene probe. Maniatis outlines a general technique for isolating a gene; it does not describe a particular DNA or cDNA molecule. Maniatis does not discuss certain steps in isolating a target cDNA, e.g., screening a tissue-specific cDNA library to obtain a cDNA and designing an oligonucleotide probe that will hybridize with the cDNA.

The examiner asserted that Bohlen's disclosure of a heparin-binding growth factor and its N-terminal sequence, and its use in gene cloning method, it was *prima facie* obvious to one of ordinary skill in the art at the time of the invention. The examiner reasoned that a person of ordinary skill in the art would have motivated a person to clone the gene for HBGF.<sup>6</sup> According to the examiner, Bohlen's published N-terminal sequence would have motivated a person of ordinary skill in the art to clone the gene for HBGF, a useful production of HBGF, a useful protein. The examiner reasoned that a per-

<sup>3</sup> European Patent Application naming Peter Bohlen as inventor, filed August 2, 1989.

<sup>4</sup> Maniatis et al., *Molecular Cloning: A Laboratory Manual*, "Screening Bacterial Libraries for Specific DNA Sequences," Cold Spring Harbor Laboratory, New York, 1982, pp. 353-361.

<sup>5</sup> Bohlen's disclosed N-terminal sequences of human and bovine HBBMs are: Glu - Lys - Pro - Glu - Lys - Lys - Ser - Asp - Cys - Gly - Lys - Glu. Deuel's disclosed N-terminal sequence of human placental HBGF is: Glu - Lys - Pro - Glu - Lys - Lys - Val - Lys - Lys - Ser - Asp - Cys - Gly - Glu - Trp - Gln - Trp - Ser - Val - Cys - Val - Pro.

<sup>2</sup> Deuel determined that the N-terminal sequence of bovine uterus HBGF is Gly - Lys - Lys - Glu - Lys - Pro - Glu - Lys - Lys - Val - Lys - Lys - Ser - Asp - Cys - Gly - Glu - Trp - Gln - Trp - Ser - Val - Cys - Val - Pro.

<sup>6</sup> The examiner and the Board used the term "gene" to refer to chromosomal DNA and synthetic DNA. The examiner will use the several terms as appropriate.

ic cDNA molecule encoding human HBGF, Deuel predicted the amino acid sequence of human BGF disclosed in Deuel's application. Deuel's application predicted human placental and bovine HBGFs each have 168 amino acids. Deuel's application calculated molecular weights of the 168 amino acids present in HBGFs discovered by Deuel, 163 are Deuel's application does not describe the chemical structure of, or state how to obtain, and purify, any DNA or cDNA except the disclosed human placental and bovine uterine cDNAs, which are the subject of claims 5 and 7.

On appeal are all independent claims, in relevant part, as follows: "a purified and isolated DNA sequence consisting of a sequence encoding a heparin binding growth factor of 168 amino acids having the following amino acid sequence:

His Ala ... [remainder of 166 amino acid sequence].

a purified and isolated cDNA of a heparin-binding growth factor having the following nucleotide sequence:

AAGGCA ... [remainder of 510 nucleotide sequence].

a purified and isolated DNA sequence consisting of a sequence encoding a heparin binding growth factor of 168 amino acids having the following amino acid sequence:

His Thr ... [remainder of 166 amino acid sequence].

a purified and isolated cDNA of a heparin-binding growth factor having the following nucleotide sequence:

GGGAGAG ... [remainder of 510 nucleotide sequence].

Claims 4 and 6 generically encompass all purified DNA sequences (natural or synthetic) encoding human and bovine HBGFs. Despite the fact that Deuel's application does not describe the chemical structure of, or state how to obtain, any DNA or cDNA except the two disclosed cDNA molecules, because of the redundancy of the claims, claims 4 and 6 each encompass a vast number of DNA molecules. Deuel isolated/purified chromosomal DNA encoding the human and bovine HBGFs in claims 5 and 7, on the other hand, are specifically disclosed cDNA molecules encoding human and bovine HBGFs respectively.

In prosecution, the examiner rejected the claims under 35 U.S.C. § 103 as unpatentable over the combined teachings of Boh-

len<sup>1</sup> and Maniatis.<sup>4</sup> The Bohlen reference discloses a group of protein growth factors designated as heparin-binding brain mitogens ("HBBMs") useful in treating burns and promoting the formation, maintenance, and repair of tissue, particularly neural tissue. Bohlen isolated three such HBBMs from human and bovine brain tissue. These proteins have respective molecular weights of 15 kD, 16 kD, and 18 kD. Bohlen determined the first 19 amino acids of the proteins' N-terminal sequences, which were found to be identical for human and bovine HBBMs.<sup>5</sup> Bohlen teaches that HBBMs are brain-specific, and suggests that the proteins may be homologous between species. The reference provides no teachings concerning DNA or cDNA coding for HBBMs.

Maniatis describes a method of isolating DNAs or cDNAs by screening a DNA or cDNA library with a gene probe. The reference outlines a general technique for cloning a gene; it does not describe how to isolate a particular DNA or cDNA molecule. Maniatis does not discuss certain steps necessary to isolate a target cDNA, e.g., selecting a tissue-specific cDNA library containing a target cDNA and designing an oligonucleotide probe that will hybridize with the target cDNA.

The examiner asserted that, given Bohlen's disclosure of a heparin-binding protein and its N-terminal sequence and Maniatis's gene cloning method, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to clone a gene for HBGF.<sup>6</sup> According to the examiner, Bohlen's published N-terminal sequence would have motivated a person of ordinary skill in the art to clone such a gene because cloning the gene would allow recombinant production of HBGF, a useful protein. The examiner reasoned that a person of ordinary

skill in the art could have designed a gene probe based on Bohlen's disclosed N-terminal sequence, then screened a DNA library in accordance with Maniatis's gene cloning method to isolate a gene encoding an HBGF. The examiner did not distinguish between claims 4 and 6 generically directed to all DNA sequences encoding human and bovine HBGFs and claims 5 and 7 reciting particular cDNAs.

In reply, Deuel argued, *inter alia*, that Bohlen teaches away from the claimed cDNA molecules because Bohlen suggests that HBBMs are brain-specific and, thus, a person of ordinary skill in the art would not have tried to isolate corresponding cDNA clones from human placental and bovine uterine cDNA libraries. The examiner made the rejection final, however, asserting that

[t]he starting materials are not relevant in this case, because it was well known in the art at the time the invention was made that proteins, especially the general class of heparin binding proteins, are highly homologous between species and tissue type. It would have been entirely obvious to attempt to isolate a known protein from different tissue types and even different species.

No prior art was cited to support the proposition that it would have been obvious to screen human placental and bovine uterine cDNA libraries for the claimed cDNA clones. Presumably, the examiner was relying on Bohlen's suggestion that HBBMs may be homologous between species, although the examiner did not explain how homology between species suggests homology between tissue types.

The Board affirmed the examiner's final rejection. In its opening remarks, the Board noted that it is "constantly advised by the patent examiners, who are highly skilled in this art, that cloning procedures are routine in the art." According to the Board, "the examiners urge that when the sequence of a protein is placed into the public domain, the gene is also placed into the public domain because of the routine nature of cloning techniques." Addressing the rejection at issue, the Board determined that Bohlen's disclosure of the existence and isolation of HBBM, a functional protein, would also advise a person of ordinary skill in the art that a gene exists encoding HBBM. The Board found that a person of ordinary skill in the art would have been motivated to isolate such a gene because the protein has useful mitogenic properties, and isolating the gene for HBBM would permit large quantities of the protein to be produced for study and possible commercial use. Like the examiner,

<sup>1</sup> European Patent Application No. 0326075, naming Peter Bohlen as inventor, published August 2, 1989.

<sup>4</sup> Maniatis et al., *Molecular Cloning: A Laboratory Manual*, "Screening Bacteriophage [lambda] Libraries for Specific DNA Sequences by Recombination in *Escherichia coli*," Cold Spring Harbor Laboratory, New York, 1982, pp. 353-361.

<sup>5</sup> Bohlen's disclosed N-terminal sequence for human and bovine HBBMs is Gly - Lys - Lys - Glu - Lys - Pro - Glu - Lys - Lys - Val - Lys - Lys - Ser - Asp - Cys - Gly - Glu - Trp - Gln. This sequence matches the first 19 amino acids of Deuel's disclosed N-terminal sequence.

<sup>6</sup> The examiner and the Board apparently used the term "gene" to refer both to natural (chromosomal) DNA and synthetic cDNA. We will use the several terms as appropriate.



the Board asserted, without explanation, that HBBMs are the same as HBGFs and that the genes encoding these proteins are identical. The Board concluded that "the Bohlen reference would have suggested to those of ordinary skill in this art that they should make the gene, and the Maniatis reference would have taught a technique for 'making' the gene with a reasonable expectation of success." Responding to Deuel's argument that the claimed cDNA clones were isolated from human placental and bovine uterine cDNA libraries, whereas the combined teachings of Bohlen and Maniatis would only have suggested screening a brain tissue cDNA library, the Board stated that "the claims before us are directed to the product and not the method of isolation. Appellants have not shown that the claimed DNA was not present in and could not have been readily isolated from the brain tissue utilized by Bohlen." Deuel now appeals.<sup>7</sup>

### DISCUSSION

Obviousness is a question of law, which we review *de novo*, though factual findings underlying the Board's obviousness determination are reviewed for clear error. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Woodruff*, 919 F.2d 1575, 1577, 16 USPQ2d 1934, 1935 (Fed. Cir. 1990). The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

On appeal, Deuel challenges the Board's determination that the applied references establish a *prima facie* case of obviousness. In response, the PTO maintains that the claimed invention would have been *prima*

*facie* obvious over the combined teachings of Bohlen and Maniatis. Thus, the appeal raises the important question whether the combination of a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, may render DNA and cDNA molecules encoding the protein *prima facie* obvious under § 103.

[1] Deuel argues that the PTO failed to follow the proper legal standard in determining that the claimed cDNA molecules would have been *prima facie* obvious despite the lack of structurally similar compounds in the prior art. Deuel argues that the PTO has not cited a reference teaching cDNA molecules, but instead has improperly rejected the claims based on the alleged obviousness of a method of making the molecules. We agree.

Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest the *claimed compounds* to a person of ordinary skill in the art. Normally a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or position isomers (e.g., *ortho v. para*).

In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. See *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*en banc*) ("structural similarity between claimed and prior art subject matter, . . . where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness"), *cert. denied*, 500 U.S. 904 (1991); *In re Grabiak*, 769 F.2d 729, 731-32, 226 USPQ 870, 872 (Fed. Cir. 1985) ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's *prima facie*

case and shift the burden of going to the applicant."); *In re Lala*, 747 F.2d 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to propose molecular modifications to arrive at the claimed compound.")

Here, the prior art does not disclose relevant cDNA molecules, let alone relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7, which might render them obvious. Maniatis suggests an allegedly obvious process to isolate cDNA molecules, but, as we will indicate below, does not focus on the subject matter of claims 5 and 7. Further, while the general idea of isolating cDNA molecules, their function, and general chemical nature may have been obvious from Bohlen's teachings, and while it is clear that some gene existed may have been clear, the precise cDNA molecule of claims 5 and 7 would not have been obvious from Bohlen's reference because Bohlen teaches proteins, not the claimed or claimed cDNA molecules. The redundancy of the genetic code precluded contemplation of the specific cDNA molecules of claims 5 and 7. Thus, one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the prior art because, until the claimed molecule was actually isolated and purified, it was highly unlikely for one of ordinary skill in the art to contemplate what was actually obtained. What cannot be conceived cannot be obvious.

The PTO's theory that one of ordinary skill in the art would have been motivated to try to do what was accomplished amounts to an impermissible hindsight invention of the claimed invention. It is the fact that claims 5 and 7 are for specific compounds, and any molecule that existed was a general one, to try to find a gene that was yet undefined and constituted many forms. A general gene that was yet undefined and constituted many forms is not necessarily make obvious a specific defined gene that is subsequently discovered as a result of that search. More is required than is not found here.

The genetic code relationships between proteins and nucleic acids does not overcome the deficiencies of the cited prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules obvious because the redundancy of the genetic code permits one to find an enormous number of DNA sequences coding for the protein. No parti-

<sup>7</sup> Deuel is supported in its appeal by an *amicus curiae* brief submitted by the Biotechnology Industry Organization and the Bay Area Science Center. Amici urge that, contrary to controlling precedent, the PTO has unlawfully adopted a *per se* rule that a gene is *prima facie* obvious when at least part of the amino acid sequence of the protein encoded by the gene is known in the prior art.

over the combined teachings of Maniatis. Thus, the appeal raises the question whether the combination of prior art reference teaching a method of cloning, together with a reference to a partial amino acid sequence of a protein, renders DNA and cDNA molecules obvious *prima facie*. 103.

Deuel argues that the PTO failed to apply the proper legal standard in determining whether the claimed cDNA molecules would be obvious *prima facie* despite the existence of naturally similar compounds in the prior art. Deuel argues that the PTO has not applied the correct obviousness standard in teaching cDNA molecules.

Deuel has improperly rejected the claim on the alleged obviousness of a claim to the molecules. We agree. Deuel claims new chemical entities in the prior art, a *prima facie* case of obviousness requires that the teachings of the prior art suggest the claimed compound to a person of ordinary skill in the art.

Deuel argues that the prior art suggests the claimed compound by a *prima facie* case of obviousness upon structural similarity, i.e., that the structural relationship between the prior art compound and the claimed compound suggests the claimed compound. Structural relationships may provide a motivation or suggestion to a person of ordinary skill to obtain new compounds.

For example, a prior art compound might suggest its homologs because they often have similar properties and chemists of ordinary skill would contemplate making them to try to obtain compounds with improved properties. A known compound may suggest its isomers, either geometric (cis vs. trans) or position isomers (ortho vs. para).

In these cases, however, the prior art does not specifically teach the claimed compound, and the question becomes whether the prior art would have suggested making the claimed compound by molecular modifications necessary to achieve the claimed invention. See *In re Ladd*, 558 F.2d 347, 351, 21 USPQ2d 1897, 1901 (Fed. Cir. 1992); *In re Dillon*, 88, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc) ("structural similarity between claimed and prior art subject matter where the prior art gives reason to make the claimed compound is a *prima facie* case of obviousness," *denied*, 500 U.S. 904 (1991); *In re Ladd*, 558 F.2d 347, 351, 21 USPQ2d 1897, 1901 (Fed. Cir. 1992); *In re Dillon*, 88, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) ("In the absence of prior art, there must be adequate support in the prior art for the [prior art] ester/thioester change in structure, in complete the PTO's *prima facie* case of obviousness.")

case and shift the burden of going forward to the applicant."); *In re Ladd*, 558 F.2d 347, 351, 21 USPQ2d 1897, 1901 (Fed. Cir. 1992); *In re Dillon*, 88, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").

Here, the prior art does not disclose any relevant cDNA molecules, let alone close relatives of the specific, structurally-defined cDNA molecules of claims 5 and 7 that might render them obvious. Maniatis suggests an allegedly obvious process for trying to isolate cDNA molecules, but that, as we will indicate below, does not fill the gap regarding the subject matter of claims 5 and 7. Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules. The redundancy of the genetic code precluded contemplation of or focus on the specific cDNA molecules of claims 5 and 7. Thus, one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.

The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. It also ignores the fact that claims 5 and 7 are limited to specific compounds, and any motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms. A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here.

The genetic code relationship between proteins and nucleic acids does not overcome the deficiencies of the cited references. A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of

these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared. We recently held in *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), that a broad genus does not necessarily render obvious each compound within its scope. Similarly, knowledge of a protein does not give one a conception of a particular DNA encoding it. Thus, *a fortiori*, Bohlen's disclosure of the N-terminal portion of a protein, which the PTO urges is the same as HBGF, would not have suggested the particular cDNA molecules defined by claims 5 and 7. This is so even though one skilled in the art knew that some DNA, albeit not in purified and isolated form, did exist. The compounds of claims 5 and 7 are specific compounds not suggested by the prior art. A different result might pertain, however, if there were prior art, e.g., a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein. See *In re Petering*, 301 F.2d 676 (CCPA 1962) (prior art reference disclosing limited genus of 20 compounds rendered every species within the genus unpatentable). That is not the case here.

The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. See *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993). In *Bell*, the PTO asserted a rejection based upon the combination of a primary reference disclosing a protein (and its complete amino acid sequence) with a secondary reference describing a general method of gene cloning. We reversed the rejection, holding in part that "[t]he PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made." *Id.*

We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs. A prior art disclosure of a process reciting a particular compound or obvious variant thereof as a product of the process is, of course, another matter, raising issues of anticipation under 35 U.S.C. § 102 as well as obviousness under § 103. Moreover, where there is prior art that suggests a claimed compound, the existence, or lack thereof, of an enabling process for making that compound is surely a factor in

any patentability determination. See *In re Brown*, 329 F.2d 1006, 141 USPQ 245 (CCPA 1964) (reversing rejection for lack of an enabling method of making the claimed compound). There must, however, still be prior art that suggests the claimed compound in order for a *prima facie* case of obviousness to be made out; as we have already indicated, that prior art was lacking here with respect to claims 5 and 7. Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Thus, Maniatis's teachings, even in combination with Bohlen, fail to suggest the claimed invention.

The PTO argues that a compound may be defined by its process of preparation and therefore that a conceived process for making or isolating it provides a definition for it and can render it obvious. It cites *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991), for that proposition. We disagree. The fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious. A substance may indeed be defined by its process of preparation. That occurs, however, when it has already been prepared by that process and one therefore knows that the result of that process is the stated compound. The process is part of the definition of the compound. But that is not possible in advance, especially when the hypothetical process is only a general one. Thus, a conceived method of preparing some undefined DNA does not define it with the precision necessary to render it obvious over the protein it encodes. We did not state otherwise in *Amgen*. See *Amgen*, 927 F.2d at 1206-9, 18 USPQ2d at 1021-23 (isolated/purified human gene held nonobvious; no conception of gene without envisioning its precise identity despite conception of general process of preparation).

We conclude that, because the applied references do not teach or suggest the claimed cDNA molecules, the final rejection of claims 5 and 7 must be reversed. See also

*Bell*, 991 F.2d at 784-85, 26 USPQ2d at 1531-32 (human DNA sequences encoding IGF proteins nonobvious over asserted combination of references showing gene cloning method and complete amino acid sequences of IGFs).

Claims 4 and 6 are of a different scope than claims 5 and 7. As is conceded by Deuel, they generically encompass all DNA sequences encoding human and bovine HBGFs. Written in such a result-oriented form, claims 4 and 6 are thus tantamount to the general idea of all genes encoding the protein, all solutions to the problem. Such an idea might have been obvious from the *complete* amino acid sequence of the protein, coupled with knowledge of the genetic code, because this information may have enabled a person of ordinary skill in the art to envision the idea of, and, perhaps with the aid of a computer, even identify all members of the claimed genus. The Bohlen reference, however, only discloses a partial amino acid sequence, and thus it appears that, based on the above analysis, the claimed genus would not have been obvious over this prior art disclosure. We will therefore also reverse the final rejection of claims 4 and 6 because neither the Board nor the patent examiner articulated any separate reasons for holding these claims unpatentable apart from the grounds discussed above.

One further matter requires comment. Because Deuel's patent application does not describe how to obtain any DNA except the disclosed cDNA molecules, claims 4 and 6 may be considered to be inadequately supported by the disclosure of the application. See generally *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.) (generic DNA sequence claims held invalid under 35 U.S.C. § 112, first paragraph), *cert. denied*, 502 U.S. 856 (1991); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (Section 112 "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). As this issue is not before us, however, we will not address whether claims 4 and 6 satisfy the enablement requirement of § 112, first paragraph, but will leave to the PTO the question whether any further rejection is appropriate.

We have considered the PTO's remaining arguments and find them not persuasive.

#### CONCLUSION

The Board's decision affirming the final rejection of claims 4-7 is reversed.

**REVERSED**

U.S. Court of Appeals  
Federal Circuit

Serco Services Co. L.P. v. Ke

No. 94-1396

Decided March 29,

#### JUDICIAL PRACTICE PROCEDURE

##### 1. Jurisdiction — Court of Appeals Federal Circuit (§405.03)

#### REMEDIES

##### Non-monetary and injunctive judgments (§505.05)

Proper relationship between declaration of patent rights under Federal Circuit Act, 28 USC later-filed infringement action, Federal Circuit to foster national responsibility of Court of Federal Circuit to foster national patent practice, and thus Federal Circuit will not defer in such case to procedural rules.

#### JUDICIAL PRACTICE PROCEDURE

##### 2. Jurisdiction — Subject matter — Case or controversy

#### REMEDIES

##### Non-monetary and injunctive judgments (§505.05)

No absolute right to declaration exists even if case satisfies jurisdictional requirement that controversy is real, since Declaratory Judgment Act, 28 USC 2201(a), specifically confers with discretion as to whether to grant declaratory judgment actions; trial court, in determining whether declaratory judgment of patent non-infringement should yield to infringement action, should apply general rule favoring forum in which suit is filed.

#### JUDICIAL PRACTICE PROCEDURE

##### 3. Jurisdiction — Subject matter — Case or controversy

#### REMEDIES

##### Non-monetary and injunctive judgments (§505.05)

Federal district court did not exercise discretion by dismissing action.

# **EXHIBIT C**

re majority of studs were never ar. (Tr. 552-55).

concealed from National Gypsum and his businesses were short tional Gypsum on royalty pay-544-48). Knorr attempted to sales by SSI of tabbed metal pproved Equal, Inc., a related any. (Pl. Ex. 79, 160, Tr.

urt concludes that there is sub- nce in the record to support a lful infringement. Based on the ircumstances, this court finds nal circumstances exist so as to ard of attorney fees to National prevailing party.

will allow an award of attorney nal Gypsum for attorney fees it orting the Sauer, et al. patents.

# Court of Appeals, Federal Circuit

In re O'Farrell

No. 87-1486

Decided August 10, 1988

## PATENTS

### 1. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Applicants' method of producing predetermined protein in stable form in host species of bacteria through genetic engineering is obvious within meaning of 35 USC 103 since reference, authored by two of three patent applicants and published more than one year prior to patent application date, contained detailed enabling methodology for practicing claimed invention, suggestion for modifying prior art to practice claimed invention, and evidence suggesting that invention could be successful, and reference thus rendered invention obvious to those of ordinary skill in art at time invention was made.

### 2. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Experimenters' use of heterologous gene coded for ribosomal RNA, which is not ordinarily translated, rather than gene coded for predetermined protein, in plasmid cloning vector for introduction into host bacteria in genetic engineering experiment, does not require finding that applicant's claimed method of producing predetermined protein in host bacteria through genetic engineering was not obvious in view of published paper describing experiment, particularly observation that hybrid messenger RNA produced by experiment was apparently translated into protein, since it would have been obvious and reasonable to conclude from such observation that if gene coded for ribosomal RNA produced "junk" or "nonsense" protein, then use of gene coded for predetermined protein would result in production of "useful" protein, as application claims.

### 3. Patentability/Validity — Obviousness — In general (§115.0901)

Rejection of patent application cannot be overturned on ground that examiner and Board of Patent Appeals and Interferences applied impermissible "obvious to try" standard, since assignment of error for application of such standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which

choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it, and since neither situation is present in instant case.

### 4. Patentability/Validity — Obviousness — In general (§115.0901)

Finding of obviousness under 35 USC 103 requires only that prior art reveal reasonable expectation of success in producing claimed invention, rather than absolute prediction of such success.

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application, serial no. 180,424, filed by Patrick H. O'Farrell, Barry O. Polisky, and David H. Gelfand. From decision of Board of Patent Appeals and Interferences affirming final rejection of application on grounds of obviousness, applicants appeal. Affirmed.

J. Bruce McCubrey of Fitch, Even, Tabin & Flannery (Virginia H. Meyer, with them on brief), San Francisco, Calif., for appellant.

Harris A. Pitlick, associate solicitor, Patent and Trademark Office (Joseph F. Nakamura, solicitor and Fred E. McKelvey, deputy solicitor, with him on brief), for appellee.

Before Markey, chief judge, and Rich and Nies, circuit judges.

Rich, J.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of heterologous DNA in Bacteria." The application was rejected under 35 USC 103 on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventors, and a publication by Bahl, Mariani & Wu 1 *Gene* 81 (1976) (Bahl). We affirm.

The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Illustrative embodiments are defined in more specific claims. For example:

Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose operon, said substantial portion of said beta-galactosidase gene being under the control of said operator, promoter and site for initiation of translation, said substantial portion of said beta-galactosidase gene lacking the normal gene termination signal, and linking a heterologous gene encoding said predetermined protein to said beta-galactosidase gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of the said beta-galactosidase gene portion so that readthrough can occur from said beta-galactosidase gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Claim 3. The method of Claim 2 wherein said *E. coli* plasmid comprises the plasmid designated pBGP120.

Although the terms in these claims would be familiar to those of ordinary skill in genetic engineering, they employ a bewildering vocabulary new to those who are not versed in molecular biology. An understanding of the science and technology on which these claims are based is essential before one can analyze and explain whether the claimed invention would have been obvious in light of the prior art.

### I. Background<sup>1</sup>

Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical reactions, major structural materials of the animal body, and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects, including appellants' claimed invention, is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently.<sup>2</sup> The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *poly-*

<sup>1</sup> Basic background information about molecular biology and genetic engineering, can be found in Alberts, Bray, Lewis, Raff, Roberts & Watson, *The Molecular Biology of the Cell*, 1-253, 385-481 (1983) [hereinafter *The Cell*]; Watson, Hopkins, Roberts, Steitz & Weiner, *The Molecular Biology of the Gene*, Vol. 1 (4th ed., 1987) 3-502 [hereinafter *The Gene*]. These standard textbooks were used to supplement the information in the glossary supplied by appellants. The description here is necessarily simplified and omits important facts and concepts that are not necessary for the analysis of this case.

<sup>2</sup> There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

*peptides*.<sup>3</sup> It is the exact sequence of the amino acids are strung together in a polypeptide chain that determine the function of a protein and its chemical properties.<sup>4</sup> Although there are many amino acids, they are strung together in specific orders to produce the hundreds of proteins found in nature.

To make a protein molecule, information about the sequence of amino acids must be assembled into a long polymeric molecule, called a *polynucleotide* (or *base*), to store the information. The subunits of the DNA are called *nucleotides*. A nucleotide consists of a sugar-containing ring component (called a *base*) linked to a 5-carbon sugar (called a *phosphate group*) attached to the 3' carbon of the sugar. Each nucleotide is composed of only four nucleotides from each other in the basic sequence. The four bases are adenine, guanine, cytosine, and thymine (abbreviated respectively as A, G, C, and T). The sequence of these bases in a polynucleotide molecule specifies which amino

<sup>3</sup> Proteins are often loosely called *polypeptides* because they are only thousands of amino acids long with chains of at least 50 amino acids. Proteins typically consist of several polypeptide chains, each consisting of several amino acids. The word "protein" is broader than "polypeptide" because it includes small chains of amino acids and large chains of amino acids. The word "polypeptide" is used here to refer to small peptides have commercial significance.

<sup>4</sup> Polypeptide chains fold up into specific three-dimensional shapes. It is the shape of the polypeptide chain that determines many chemical properties of a protein. However, the configuration of a polypeptide chain is determined by its amino acid sequence. See *The Cell* at 111-12; *The Gene* at 50.

<sup>5</sup> The sugar in DNA is deoxyribose. The sugar in RNA, *infra*, is ribose. The phosphate groups are linked covalently to adjacent nucleotides to form the backbone of the long unbranched DNA molecule. The backbone is subject to the chain, and serve as the genetic code.

DNA molecules actually consist of two tightly entwined strands. The two strands are not identical but instead are complementary. Each A on one chain is paired with a T on the other chain, and each C has a G on the other chain. The two chains are held together by hydrogen bonds between these complementary bases. The helical structure plays an essential role in the replication of DNA and the transmission of genetic information. See generally *The Gene* at 65-79. However, only one strand is used for transcription, and it is not necessary to replicate the double-stranded DNA. RNA molecules, *infra*, are

3. The method of Claim 2 where-  
coli plasmid comprises the plas-  
mated pBGP120.

the terms in these claims would  
to those of ordinary skill in genet-  
ing, they employ a bewildering  
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t.

#### I. Background<sup>1</sup>

are biological molecules of enor-  
tance. Proteins include enzymes  
e biochemical reactions, major  
aterials of the animal body, and  
ones. Numerous patents and ap-  
r patents in the field of biotech-  
lve specific proteins or methods  
and using proteins. Many valu-  
s occur in nature only in minute  
or are difficult to purify from  
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ention, is to devise methods to  
seful quantities of specific pro-  
trolling the mechanism by which  
nake proteins.

organization of all proteins is  
roteins are large polymeric mole-  
ing of chains of smaller building  
d *amino acids*, that are linked  
valently.<sup>2</sup> The chemical bonds  
o acids together are called *pep-*  
so proteins are also called *poly-*

ground information about molecu-  
d genetic engineering, can be found  
ay, Lewis, Raff, Roberts & Watson,  
'ar *Biology of the Cell*, 1-253,  
3) [hereinafter *The Cell*]; Watson,  
erts, Steitz & Weiner, *The Molecu-*  
*f the Gene*, Vol. 1 (4th ed., 1987)  
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re is necessarily simplified and omits  
ts and concepts that are not neces-  
alysis of this case.

twenty amino acids: alanine, va-  
isoleucine, proline, phenylalanine,  
yptophan, glycine, asparagine, glu-  
te, serine, threonine, tyrosine, aspar-  
amic acid, lysine, arginine, and

*peptides*.<sup>3</sup> It is the exact sequence in which  
the amino acids are strung together in a  
polypeptide chain that determines the identi-  
ty of a protein and its chemical characteris-  
tics.<sup>4</sup> Although there are only 20 amino  
acids, they are strung together in different  
orders to produce the hundreds of thousands  
of proteins found in nature.

To make a protein molecule, a cell needs  
information about the sequence in which the  
amino acids must be assembled. The cell uses  
a long polymeric molecule, DNA (deoxyri-  
bonucleic acid), to store this information.  
The subunits of the DNA chain are called  
*nucleotides*. A nucleotide consists of a nitro-  
gen-containing ring compound (called a  
*base*) linked to a 5-carbon sugar that has a  
phosphate group attached.<sup>5</sup> DNA is com-  
posed of only four nucleotides. They differ  
from each other in the base region of the  
molecule. The four bases of these subunits  
are adenine, guanine, cytosine, and thymine  
(abbreviated respectively as A, G, C and T).  
The sequence of these bases along the DNA  
molecule specifies which amino acids will be

<sup>1</sup> Proteins are often loosely called *peptides*, but  
technically proteins are only the larger peptides  
with chains of at least 50 amino acids, and more  
typically hundreds of amino acids. Some proteins  
consist of several polypeptide chains bound togeth-  
er covalently or noncovalently. The term "pep-  
tide" is broader than "protein" and also includes  
small chains of amino acids linked by peptide  
bonds, some as small as two amino acids. Certain  
small peptides have commercial or medical  
significance.

<sup>2</sup> Polypeptide chains fold up into complex 3-di-  
mensional shapes. It is the shape that actually  
determines many chemical properties of the pro-  
tein. However, the configuration of a protein mole-  
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<sup>3</sup> The sugar in DNA is deoxyribose, while the  
sugar in RNA, *infra*, is ribose. The sugar and  
phosphate groups are linked covalently to those of  
adjacent nucleotides to form the backbone of the  
long unbranched DNA molecule. The bases pro-  
ject from the chain, and serve as the "alphabet" of  
the genetic code.

<sup>4</sup> DNA molecules actually consist of two chains  
tightly entwined as a double helix. The chains are  
not identical but instead are complementary: each  
A on one chain is paired with a T on the other  
chain, and each C has a corresponding G. The  
chains are held together by noncovalent bonds  
between these complementary bases. This double  
helical structure plays an essential role in the  
replication of DNA and the transmission of genet-  
ic information. See generally *The Cell* at 98-106;  
*The Gene* at 65-79. However, the information of  
only one strand is used for directing protein syn-  
thesis, and it is not necessary to discuss the impli-  
cation of the double-stranded structure of DNA  
here. RNA molecules, *infra*, are single stranded.

inserted in sequence into the polypeptide  
chain of a protein.

DNA molecules do not participate direct-  
ly in the synthesis of proteins. DNA acts as a  
permanent "blueprint" of all of the genetic  
information in the cell, and exists mainly in  
extremely long strands (called *chromo-*  
*somes*) containing information coding for  
the sequences of many proteins, most of  
which are not being synthesized at any par-  
ticular moment. The region of DNA on the  
chromosome that codes for the sequence of a  
single polypeptide is called a *gene*.<sup>6</sup> In order  
to *express* a gene (the process whereby the  
information in a gene is used to synthesize  
new protein), a copy of the gene is first made  
as a molecule of RNA (ribonucleic acid).

RNA is a molecule that closely resembles  
DNA. It differs, however in that it contains a  
different sugar (ribose instead of deoxyri-  
bose) and the base thymine (T) of DNA is  
replaced in RNA by the structurally similar  
base, uracil (U). Making an RNA copy of  
DNA is called *transcription*. The tran-  
scribed RNA copy contains sequences of A,  
U, C, and G that carry the same information  
as the sequence of A, T, C, and G in the  
DNA. That RNA molecule, called *messen-*  
*ger RNA*, then moves to a location in the cell  
where proteins are synthesized.

The code whereby a sequence of nucle-  
otides along an RNA molecule is translated  
into a sequence of amino acids in a protein  
(i.e., the "genetic code") is based on serially  
reading groups of three adjacent nucleotides.  
Each combination of three adjacent nucle-  
otides, called a *codon*, specifies a particular  
amino acid. For example, the codon U-G-G  
in a messenger RNA molecule specifies that  
there will be a tryptophan molecule in the  
corresponding location in the corresponding  
polypeptide. The four bases A, G, C and U  
can be combined as triplets in 64 different  
ways, but there are only 20 amino acids to be  
coded. Thus, most amino acids are coded for  
by more than one codon. For example, both  
U-A-U and U-A-C code for tyrosine, and  
there are six different codons that code for  
leucine. There are also three codons that do  
not code for any amino acid (namely, U-A-  
A, U-G-A, and U-A-G). Like periods at the  
end of a sentence, these sequences signal the  
end of the polypeptide chain, and they are  
therefore called *stop codons*.

<sup>6</sup> Chromosomes also contain regions of DNA  
that are not part of genes, i.e., do not code for the  
sequence of amino acids in proteins. These include  
sections of DNA adjacent to genes that are in-  
volved in the control of transcription, *infra*, and  
regions of unknown function.



The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules "read" the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome. When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome.

The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*. A messenger RNA molecule is typically reused to make many copies of the same protein. Synthesis of a protein is usually terminated by destroying the messenger RNA. (The information for making more of that protein remains stored in DNA in the chromosomes.)

The translation of messenger RNA begins at a specific sequence of nucleotides that bind the RNA to the ribosome and specify which is the first codon that is to be translated. Translation then proceeds by reading nucleotides, three at a time, until a stop codon is reached. If some error were to occur that shifts the frame in which the nucleotides are read by one or two nucleotides, all of the codons after this shift would be misread. For example, the sequence of codons [... C-U-C-A-G-C-G-U-U-A-C-C-A...] codes for the chain of amino acids [... leucine-serine-valine-threonine...]. If the reading of these groups of three nucleotides is displaced by one nucleotide, such as [... C-U-C-A-G-C-G-U-U-A-C-C-A...], the resulting peptide chain would consist of [... serine-alanine-leucine-proline...]. This would be an entirely different peptide, and most probably an undesirable and useless one. Synthesis of a particular protein requires that the correct register or *reading frame* be maintained as the codons in the RNA are translated.

The function of messenger RNA is to carry genetic information (transcribed from DNA) to the protein synthetic machinery of a cell where its information is translated into the amino acid sequence of a protein. However, some kinds of RNA have other roles. For example, ribosomes contain several large strands of RNA that serve a structural function (*ribosomal RNA*). Chromosomes contain regions of DNA that code for the nucleotide sequences of structural RNAs and these sequences are transcribed to manufacture those RNAs. The DNA sequences coding for structural RNAs are still called genes

even though the nucleotide sequence of the structural RNA is never translated into protein.

Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Bacteria (*procaryotic* or prokaryotic organisms) have a different organization. Their DNA, usually a circular loop, is not contained in any specialized compartment. Despite the incredible differences between them, all organisms, whether eucaryote or procaryote, whether man or mouse or lowly bacterium, use the same molecular rules to make proteins under the control of genes. In all organisms, codons in DNA are transcribed into codons in RNA which is translated on ribosomes into polypeptides according to the same genetic code. Thus, if a gene from a man is transferred into a bacterium, the bacterium can manufacture the human protein. Since most commercially valuable proteins come from man or other eucaryotes while bacteria are essentially little biochemical factories that can be grown in huge quantities, one strategy for manufacturing a desired protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the gene normally occurs into a bacterium.

Bacteria containing genes from a foreign source (*heterologous* genes) integrated into their own genetic makeup are said to be *transformed*. When transformed bacteria grow and divide, the inserted heterologous genes, like all the other genes that are normally present in the bacterium (*indigenous* genes), are replicated and passed on to succeeding generations. One can produce large quantities of transformed bacteria that contain transplanted heterologous genes. The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein. This is the purpose of the claimed invention.

In order to make a selected protein by expressing its cloned gene in bacteria, several technical hurdles must be overcome. First the gene coding for the specific protein must be isolated for cloning. This is a formidable task, but recombinant DNA technology has armed the genetic engineer with a variety of

techniques to accomplish it.<sup>7</sup> No cloned gene must be introduced into a bacterium. This can be done by inserting the gene into a cloning vector. A *vector* is a piece of DNA that is introduced into bacteria and will then itself as the bacterial cells grow. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but were the type used by appellants is a small circular loop of DNA that replicates like a chromosome, but contains only a few genes. Because of their plasmids are convenient for the biologist to isolate and work with, and DNA technology can be used to splice plasmids by splicing in cloned genes and other useful segments containing control sequences. Such DNA can even be designed to have specific nucleotide sequences, synthesized, and spliced into the plasmid, such chemically synthesized linear DNA, to ensure that the inserted gene has the same reading frame as the rest of the plasmid. This is a teaching of the Bahl reference against appellants. A plasmid can be used by the molecular geneticist can be used in bacteria, where it replicates as a plasmid and grows.

Even after a cloned heterologous gene has been successfully inserted into a plasmid as a cloning vector, as the bacteria grow, there is a risk that the gene will be expressed and translated into protein. For example, *E. coli* (the species of bacterium used by appellants) has several thousand proteins. At a minimum many of those genes are not expressed at all. The genetic engineer must induce the cloned gene to "turn on" the cloned gene to be expressed. This is the problem appellants worked to solve.

## II. Prior art

Appellants sought to control the expression of cloned heterologous genes in bacteria. They reported that their early efforts in a publication by two authors of which included two coinventor-appellants (the Polisky and Gelfand), that is undisputed prior art.

<sup>7</sup> See *The Cell* at 185-194; 208-10.

<sup>8</sup> Polisky, Bishop & Gelfand, *A cloning vehicle allowing regulated expression of eucaryotic DNA in bacteria*, 73 Proc. Nat'l. Acad. Sci. USA 3900 (1976).



h the nucleotide sequence of the RNA<sup>7</sup> is never translated into

ner animals, plants, protozoa, and eucaryotic (or eukaryotic) organisms. DNA is packaged in chromosomal special compartment of the cell, i. Bacteria (prokaryotic or prokaryotes) have a different organization. DNA, usually a circular loop, is found in any specialized compartment. The incredible differences between, all organisms, whether eucaryote, whether man or mouse or bacterium, use the same molecular mechanisms to control the expression of all organisms, codons in DNA are translated into codons in RNA which are then translated into polypeptides of the same genetic code. Thus, if a man is transferred into a bacterium can manufacture protein. Since most commercially available proteins come from man or other sources while bacteria are essentially little factories that can be grown in quantities, one strategy for manufacturing protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the protein occurs into a bacterium.

containing genes from a foreign source (heterologous genes) integrated into the genetic makeup are said to be recombinant. When transformed bacteria divide, the inserted heterologous genes along with all the other genes that are normally present in the bacterium (indigenous genes) are replicated and passed on to successive generations. One can produce large quantities of transformed bacteria that contain cloned heterologous genes. The making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells growing those cells is called cloning. After growing sufficient quantities of the transformed bacteria, the genetic engineer must induce the transformed bacteria to express the cloned gene and produce large quantities of the protein. This is the gist of the claimed invention.

to make a selected protein by inserting a cloned gene in bacteria, several hurdles must be overcome. First, finding for the specific protein must be done. This is a formidable task. Combinant DNA technology has enabled the genetic engineer with a variety of

techniques to accomplish it.<sup>7</sup> Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A cloning vector is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but plasmids were the type used by appellants. A plasmid is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. It is like a tiny auxiliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with. Recombinant DNA technology can be used to modify plasmids by splicing in cloned eucaryotic genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into the plasmid. One use of such chemically synthesized linkers is to insure that the inserted gene has the same reading frame as the rest of the plasmid; this is a teaching of the Bahl reference cited against appellants. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow.

Even after a cloned heterologous gene has been successfully inserted into bacteria using a plasmid as a cloning vector, and replicates as the bacteria grow, there is no guarantee that the gene will be expressed, i.e., transcribed and translated into protein. A bacterium such as *E. coli* (the species of bacterium used by appellants) has genes for several thousand proteins. At any given moment many of those genes are not expressed at all. The genetic engineer needs a method to "turn on" the cloned gene and force it to be expressed. This is the problem appellants worked to solve.

## II. Prior art

Appellants sought to control the expression of cloned heterologous genes inserted into bacteria. They reported the results of their early efforts in a publication, the three authors of which included two of the three coinventor-appellants (the Polisky reference<sup>8</sup>), that is undisputed prior art against

them. Their strategy was to link the foreign gene to a highly regulated indigenous gene. Turning on expression of the indigenous gene by normal control mechanisms of the host would cause expression of the linked heterologous gene.

As a controllable indigenous gene, the researchers chose a gene in the bacterium *E. coli* that makes beta-galactosidase. Beta-galactosidase is an enzyme needed to digest the sugar, lactose (milk sugar). When *E. coli* grows in a medium that contains no lactose, it does not make beta-galactosidase. If lactose is added to the medium, the gene coding for beta galactosidase is expressed. The bacterial cell makes beta-galactosidase and is then able to use lactose as a food source. When lactose is no longer available, the cell again stops expressing the gene for beta galactosidase.

The molecular mechanisms through which the presence of lactose turns on expression of the beta-galactosidase gene has been studied in detail, and is one of the best understood examples of how gene expression is regulated on the molecular level. The beta-galactosidase gene is controlled by segments of DNA adjacent to the gene. These regulatory DNA sequences (the general term used in Claim 1) include the operator and promoter sequences (specified in Claim 2).<sup>9</sup> The researchers constructed a plasmid containing the beta-galactosidase gene with its operator and promoter. This gene (with its regulatory sequences) was removed from the chromosome of *E. coli* where it is normally found and was transplanted to a plasmid that could be conveniently manipulated.

Restriction endonucleases are useful tools in genetic engineering. These enzymes cut strands of DNA, but only at places where a specific sequence of nucleotides is present. For example, one restriction endonuclease, called *EcoRI*, cuts DNA only at sites where

<sup>7</sup> The promoter is a sequence of nucleotides where the enzyme that synthesizes RNA, RNA polymerase, attaches to the DNA to start the transcription of the beta-galactosidase gene. The operator is an overlapping DNA sequence that binds a small protein present in the cell, the lactose repressor protein. The lactose repressor protein binds to the operator and physically blocks the RNA polymerase from properly attaching to the promoter so that transcription cannot proceed. Lactose molecules interact with the lactose repressor protein and cause it to change its shape; after this change in shape it moves out of the way and no longer prevents the RNA polymerase from binding to the promoter. Messenger RNA coding for beta-galactosidase can then be transcribed. See generally *The Cell* at 438-39; *The Gene* at 474-80.

<sup>8</sup> See *The Cell* at 185-194; *The Gene* at 208-10.

<sup>9</sup> Polisky, Bishop & Gelfand, *A plasmid cloning vehicle allowing regulated expression of eucaryotic DNA in bacteria*, 73 Proc. Nat'l Acad. Sci. USA 3900 (1976).

the nucleotide sequence is [...G-A-A-T-T-C...]. With restriction enzymes the genetic engineer can cut a strand of DNA at very specific sites into just a few pieces. With the help of "repair" enzymes, other pieces of DNA can be spliced onto the cut ends. The investigators found that the plasmid which they had constructed contained only two sequences that were cut by EcoRI. They were able to eliminate one of these sites that was unwanted. They were then left with a plasmid containing the beta-galactosidase gene with its regulatory sequences, and a single EcoRI site that was within the beta-galactosidase gene and close to its stop codon. They named this plasmid that they had constructed pBGP120.

The next step was to cut the plasmid open at its EcoRI site and insert a heterologous gene from another organism. The particular heterologous gene they chose to splice in was a segment of DNA from a frog that coded for ribosomal RNA. The frog gene was chosen as a test gene for reasons of convenience and availability. The new plasmid created by inserting the frog gene was similar to pBGP120, but its beta-galactosidase gene was incomplete. Some codons including the stop codon were missing from its end, which instead continued on with the sequence of the frog ribosomal RNA gene. The investigators named this new plasmid pBGP123. They inserted this plasmid back into *E. coli* and grew sufficient quantities for study. They then fed the *E. coli* with lactose. As they had intended, the lactose turned on transcription of the beta-galactosidase gene in the plasmid. RNA polymerase moved along the plasmid producing a strange new kind of RNA: Each long strand of RNA first contained codons for the messenger RNA for beta-galactosidase and then continued without interruption with the codons for the frog ribosomal RNA. Thus, there was *readthrough* transcription in which the RNA polymerase first transcribed the indigenous (beta-galactosidase) gene and then "read through," i.e., continued into and through the adjacent heterologous (frog ribosomal RNA) gene. Although the RNA produced was a hybrid, it nevertheless contained a nucleotide sequence dictated by DNA from a frog. The researchers had achieved the first controlled transcription of an animal gene inside a bacterium.

The researchers had used a gene coding for a ribosomal RNA as their heterologous test gene. Ribosomal RNA is not normally translated into protein. Nevertheless, they were obviously interested in using their approach to make heterologous proteins in bacteria. They therefore examined the beta-

galactosidase made by their transformed bacteria. Patrick O'Farrell, who was not a coauthor of the Polisky paper but was to become a coinventor in the patent application, joined as a collaborator. They found that beta-galactosidase from the transformed bacteria had a higher molecular weight than was normal. They concluded that the bacteria must have used their strange new hybrid RNA like any other messenger RNA and translated it into protein. When the machinery of protein synthesis reached the premature end of the sequence coding for beta-galactosidase it continued right on, three nucleotides at a time, adding whatever amino acid was coded for by those nucleotides, until a triplet was reached with the sequence of a stop codon. The resulting polypeptide chains had more amino acids than normal beta-galactosidase, and thus a higher molecular weight. The researchers published their preliminary results in the Polisky article. They wrote:

[I]f the normal translational stop signals for [beta]-galactosidase are missing in pBGP120, in-phase translational readthrough into adjacent inserted sequences might occur, resulting in a significant increase in the size of the [beta]-galactosidase polypeptide subunit. In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of *Xenopus* [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Polisky at 3904.

Since ribosomal RNA is never translated in normal cells, the polypeptide chain produced by translating that chain was not a naturally occurring, identified protein. The authors of the Polisky paper explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain:

It would be interesting to examine the expression of a normally translated eukaryotic sequence in pBGP120. If an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide. In the absence of an independent ribosome bind-

ing site, the eukaryotic sequence translated to yield a peptide linked to [beta]-galactosidase. of readthrough translation and control will depend on the number of available codons between the EcoRI the first in-phase nonsense [i.e. don in the inserted sequence.

*Id.*

### III. The Claimed Invention

Referring back to Claims 1 through 4, it can be seen that virtually every claim was present in the prior art. The main difference is that the heterologous gene was a gene for a ribosomal RNA while the claimed invention substitutes a gene coding for a protein. Ribosomal RNA gene is normally translated into protein, so even if the heterologous gene was studied in terms of transcription into RNA, less, Polisky mentioned preliminarily that the transcript of the ribosomal gene was translated into protein. He further predicted that if a gene that coded for a protein were to be substituted for a ribosomal RNA gene, "a readthrough transcript might allow for extensive of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art. There is no preliminary evidence that the method could be used to produce proteins.

Appellants reduced their invention to practice some time in 1976 and published their results in a paper that was published in 1978.<sup>10</sup> During 1977 they conducted their results to another group of scientists who used the readthrough transcript to achieve the first synthesis of a functional eukaryotic polypeptide.

<sup>10</sup> O'Farrell, Polisky & Gelfand, *Repression by readthrough translation of mid-encoded beta-galactosidase*, 134 F.2d 645 (1978). The heterologous genes used in these studies were not predetermined but were unidentified genes of unknown function. The authors speculated that they were plasmids from *E. coli* that were contaminants of beta-galactosidase genes. *Id.* at 6.

made by their transformed "ck O'Farrell, who was not a Polisky paper but was a inventor in the patent application; a collaborator. They found galactosidase from the trans-ia had a higher molecular weight than normal. They concluded bacteria must have used their hybrid RNA like any other A and translated it into protein machinery of protein synthesis. The premature end of the sequence for beta-galactosidase is at it on, three nucleotides at a whatever amino acid was coded nucleotides, until a triplet was the sequence of a stop codon. polypeptide chains had more an normal beta-galactosidase, higher molecular weight. They blished their preliminary review in a Polisky article. They wrote: "Normal translational stop signals for beta-galactosidase are missing in in-phase translational reading of adjacent inserted sequences, resulting in a significant increase in size of the [beta]-galactosidase subunit. In fact, we have observed that induced cultures of contain elevated levels of beta-galactosidase of higher subunit molecular weight than wild-type enzyme (Polisky unpublished experiments). We observed an increase in results from translation of [frog] RNA sequences linked to [messenger] RNA for beta-galactosidase, resulting in a fused

4. The normal RNA is never translated as a polypeptide chain. Polishing that chain was not a protein, identified protein. The Polisky paper explicitly pointed out that one were to insert a heterologous gene for a protein into their plasmid would produce a "fused protein" and a polypeptide made of beta-galactosidase plus the protein coded for by the gene, joined by a peptide bond and a continuous polypeptide chain:

"It is interesting to examine the effect of a normally translated eukaryotic gene in pBGP120. If an inserted gene contains a ribosome binding site and is utilized in bacteria, production of a readthrough transcript for extensive translation of a eukaryotic polypeptide. In the absence of an independent ribosome bind-

ing site, the eukaryotic sequence would be translated to yield a peptide covalently linked to [beta]-galactosidase. The extent of readthrough translation under *lac* control will depend on the number of translatable codons between the EcoRI site and the first in-phase nonsense [i.e., stop] codon in the inserted sequence.

*Id.*

### III. The Claimed Invention

Referring back to Claims 1 through 3, it can be seen that virtually everything in the claims was present in the prior art Polisky article. The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly in terms of transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

Appellants reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978.<sup>10</sup> During 1977 they communicated their results to another group of researchers who used the readthrough translation approach to achieve the first synthesis of a

human protein in bacteria.<sup>11</sup> Appellants filed an application to patent their invention on August 9, 1978, of which the application on appeal is a division.

### IV. The Obviousness Rejection

The application was rejected under 35 USC 103. The position of the examiner and the Board is, simply, that so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made.

The claims specify that the heterologous gene should be inserted into the plasmid in the same orientation and with the same reading frame as the preceding portion of the indigenous gene. In view of this limitation, the §103 rejection was based either on Polisky alone (supplemented by the fact that the importance of orientation and reading frame was well known in the prior art) or in combination with the Bahl reference which describes a general method for inserting a piece of chemically synthesized DNA into a plasmid. Bahl teaches that this technique could be used to shift the sequence of DNA inserted into a plasmid into the proper reading frame.

Appellants argue that at the time the Polisky article was published, there was significant unpredictability in the field of molecular biology so that the Polisky article would not have rendered the claimed method obvious to one of ordinary skill in the art. Even though there was speculation in the article that genes coding for proteins could be substituted for the ribosomal RNA gene and would be expressed as readthrough translation into the protein, this had never been done. Appellants say that it was not yet certain whether a heterologous protein could actually be produced in bacteria, and if it could, whether additional mechanisms or methods would be required. They contend

<sup>10</sup> O'Farrell, Polisk & Gelfand, *Regulated expression by readthrough translation from a plasmid-encoded beta-galactosidase*, 134 J. Bacteriol. 645 (1978). The heterologous genes expressed in these studies were not predetermined, but were instead unidentified genes of unknown origin. The authors speculated that they were probably genes from *E. coli* that were contaminants in the source of beta-galactosidase genes. *Id.* at 648

<sup>11</sup> Itakura, Hirose, Crea, Riggs, Heynecker, Bolivar & Boyer, *Expression in Escherichia coli of a chemically synthesized gene for the hormone somatostatin*, 198 Science 1056 (1977). A pioneering accomplishment of the Itakura group is that the gene was not from a human source, but instead was entirely synthesized in the laboratory using chemical methods. It is not clear whether the appellants communicated only the results reported in the Polisky publication or whether they communicated the complete claimed invention.

that without such certainty the predictions in the Polisky paper, which hindsight now shows to have been correct, were merely invitations to those skilled in the art to try to make the claimed invention. They argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a §103 rejection. *E.g.*, *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

Obviousness under §103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 107 S.Ct. 2187 (1987). An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). *See, e.g.*, *Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 958, 1 USPQ2d 1196, 1197 (Fed. Cir. 1986). The scope and content of the prior art and the differences between the prior art and the claimed invention have been examined in sections II and III, *supra*. Appellants say that in 1976 those of ordinary skill in the arts of molecular biology and recombinant DNA technology were research scientists who had "extraordinary skill in relevant arts" and "were among the brightest biologists in the world." Objective evidence of nonobviousness was not argued.

[1] With the statutory factors as expounded by *Graham* in mind and considering all of the evidence, this court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. We agree with the board that appellants' claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl within the meaning of §103. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

[2] Appellants argue that after the publication of Polisky, successful synthesis of protein was still uncertain. They belittle the predictive value of the observation that expression of the transcribed RNA in Polisky produced beta-galactosidase with a greater than normal molecular weight, arguing that since ribosomal RNA is not normally translated, the polypeptide chains that were added to the end of the beta-galactosidase were "junk" or "nonsense" proteins. This characterization ignores the clear implications of the reported observations. The Polisky study directly proved that a readthrough transcript messenger RNA had been produced. The preliminary observation showed that this messenger RNA was read and used for successful translation. It was well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered. The preliminary observations thus showed that codons beyond the end of the beta-galactosidase gene were being translated into peptide chains. This would reasonably suggest to one skilled in the art that if the codons inserted beyond the end of the beta-galactosidase gene coded for a "predetermined protein," that protein would be produced. In other words, it would have been obvious and reasonable to conclude from the observation reported in Polisky that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result. The relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long.<sup>12</sup>

Appellants complain that since predetermined proteins had not yet been produced in transformed bacteria, there was uncertainty as to whether this could be done, and that the rejection is thus founded on an impermissible "obvious to try" standard. It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometime lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an

<sup>12</sup> The patent application indicates that chains as long as 60 amino acids were added, which is hardly a trivial length of polypeptide.

invention that was obvious to less nonobvious?

[3] The admonition that "obvious to try" is not the standard under §103 is directed mainly at two kinds of cases. In some cases, what would have been "obvious to try" would have been to vary parameters or try each of numerous choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameter was better or no direction as to which possible choices is likely to be better. *E.g.*, *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278; *Novo Ind. Travenol Laboratories, Inc.*, 672 F.2d 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1055, 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977). In what was "obvious to try" was new technology or general art that seemed to be a promising field of investigation, where the prior art gave guidance as to the particular claimed invention or how to achieve it. *Dow Chemical Co.*, 837 F.2d 1529, 1532 (Fed. Cir. 1987); *Britech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 623, 626 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987); *In re Tomlinson*, 831 F.2d 150, 155 USPQ 623, 626 (CCPA 1987). Neither of these situations apply here.

[4] Obviousness does not require predictability of success. Inventions that seem quite obvious to try have no absolute predictability of success. Invention is reduced to practicality, always at least a possibility of success, results, that would then provide a basis for showing that the invention was, though apparently obvious, was not obvious. *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); *Linchinfabrik GmbH v. American Derrick Co.*, 730 F.2d 145, 148, 488 (Fed. Cir. 1984); *Papesch*, 315 F.2d 381, 386-87, 47-48 (CCPA 1963). For purposes of §103, all that is required is a reasonable expectation of success. *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977); *In re Clinton*, 572 F.2d 1228, 188 USPQ 365, 367 (Fed. Cir. 1977). The information in the Polisky reference when combined with the Bahl reference would provide such a reasonable expectation of success.

Appellants published the results of the expression of foreign DNA genes in bacteria mor-

lants argue that after the publication, successful synthesis of polypeptides is uncertain. They belittle the value of the observation that exogenous RNA in Polisky's beta-galactosidase with a greater molecular weight, arguing that exogenous RNA is not normally transcribed into polypeptide chains that were added to the beta-galactosidase were "nonsense" proteins. This characterizes the clear implications of observations. The Polisky study showed that a readthrough transcript of RNA had been produced. The observation showed that this RNA was read and used for translation. It was well known in the field that ribosomal RNA was made of the same as messenger RNA, that a sequence of nucleotides could be read in three as codons, and that reading should specify a polypeptide chain. The preliminary observation showed that codons beyond the beta-galactosidase gene were added into peptide chains. This might suggest to one skilled in the art that the codons inserted beyond the beta-galactosidase gene coded for "nonsense" protein, that protein produced. In other words, it would be obvious and reasonable to conclude the observation reported in Polisky that nonsense RNA produced polypeptides, if meaningful RNA instead of ribosomal RNA, use could be the result. The relative length of the added chains is also not a certainty, since one skilled in the art would know that a random sequence of nucleotides would produce a stop codon if the chain got too long.<sup>12</sup>

Appellants complain that since predeterminations had not yet been produced in bacteria, there was uncertainty as to whether this could be done, and that the test was founded on an impermissible "obvious to try" standard. It is true that this test's predecessors have repeatedly stated that "obvious to try" is not the proper standard under §103. However, the meaning of §103 is sometime lost. Any invention would in fact have been obvious if it could also have been, in a sense, obvious. The question is: when is an

<sup>12</sup> Application indicates that chains of amino acids were added, which is the length of polypeptide.

invention that was obvious to try nevertheless nonobvious?

[3] The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). Neither of these situations applies here.

[4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law non-obvious. *In re Merck & Co.*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); *In re Papesch*, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success.

Appellants published their pioneering studies of the expression of frog ribosomal RNA genes in bacteria more than a year

before they applied for a patent. After providing virtually all of their method to the public without applying for a patent within a year, they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary skill in the art, with or without the disclosures of other prior art. The decision of the board is

**AFFIRMED.**

District Court, W.D. Washington

Specialized Electronics Corp. v. Aviation Supplies & Academics Inc.

No. C86-712D

Decided March 23, 1988

## PATENTS

### 1. Patentability/Validity — Obviousness — Secondary considerations (§115.0907)

Patent infringement defendant has failed to sustain its burden of proving, by clear and convincing evidence, that claims for hand-held aircraft navigational computers are invalid for obviousness under 35 USC 103, in view of objective evidence of secondary considerations demonstrating non-obviousness.

### 2. Infringement — Defenses — Prosecution history estoppel (§120.1105)

Doctrine of prosecution history estoppel applies to arguments narrowing construction of claims even if claims are not amended.

### 3. Patent construction — Claims — Broad or narrow (§125.1303)

Doctrine of claim differentiation precludes reading into independent claim limitation explicitly set forth in another claim, and such doctrine, although it is useful tool of claim construction, cannot be used to repudiate arguments made to Patent and Trademark Office in order to obtain allowance of asserted claims over prior art.

### Particular patents — General and mechanical — Computers

3,979,057, Katz, Aronson, and Turek, self-contained hand-held electronic computer for aircraft navigation problems, claim 27 valid but not infringed.

3,979,058, Katz, Aronson, and Turek, self-contained electronic computer for math-